Drug Discovery Shared Resource

Director: Shengliang Zhang MD, PhD

LEGORRETA CANCER CENTER
BROWN UNIVERSITY

Overview

The capability of small molecule drug screening has accelerated drug discovery prospects within academic institutions, and this has enabled translational goals with further development towards clinical trials.We have set-up a high-throughput robotic screening capability for a 96-well or 384-well format and this has been used to screen large libraries of small molecules. Screens have led to lead compounds including some that have been successfully translated to clinical trials.

Key Services

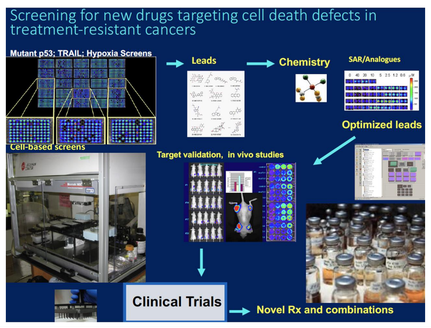
- Design phenotypic cell-based screens using chemical libraries
- Quantitative optical imaging readouts
- Access to robotic instrumentation
- Access to chemical libraries
- Primary and secondary drug screens
- Target validation
- Consultations

Value Added

Advise investigators on cancer drug screens, cell-based assay development, assay optimization, and use of various chemical libraries to support research in the area of drug discovery and development.
Advise on target validation and interface with medicinal chemistry.
Provide technical support for screening implementation, library plating, high-throughput robotic screening
Advice on prioritization of hits.
Provide support for grant submissions.

Major Equipment /Technologies

- Biomek Laboratory automation workstation for liquid handling
- ImageXpress Confocal HT. ai. plate reader
- IVIS imaging multiple plate reader



Key Personnel

Director: Shengliang Zhang MD, PhD
Assistant Professor of Pathology and Laboratory Medicine (Research)

Examples of Scientific Impact

Drug Discovery

High-throughput screening for drugs targeting cancer using cell- based assay

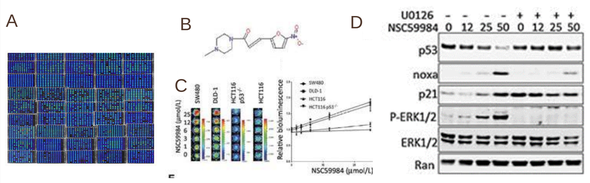


Figure 1. **Identification of a small-Molecule NSC59984 as an antitumor lead that Induces mutant p53 degradation through a ROS-ERK2-MDM2 sxis in Cancer Cells**

Investigators: Zhang S., Zhou L., and El-Deiry WS.
Citations: 119 citations

Drug screening for treating COVID-19

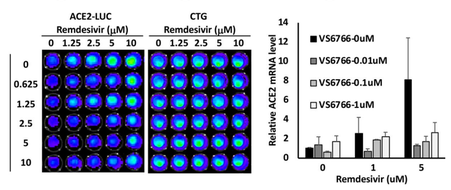


Figure 2. **MEK inhibitors alone or in combination with remdesivir suppress ACE2 expression**

Collaborators: Zhou L., Huntington K., Zhang S., Carlsen L., So E., Parker C., Sahin I., Safran H., Kamle S., Lee C., Lee C. Elias J.A., Campbell K.S., Naik M.T., Atwood W.J., Youssef E., Pachter J. A., Navaraj A., Seyhan A.A., Liang O., and El-Deiry W.S
Funding: Brown University COVID-19 Seed Grant (to W.S.E-D.)
Citations: 29 citations

Consultations and assay optimizations for Heclin analogue secondary screens under hypoxia

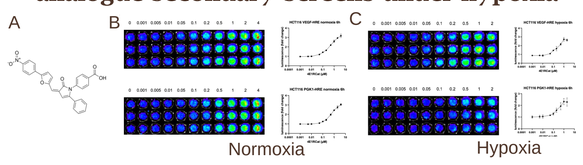


Figure 3. **Analogue 4E1RCat induces HIF-1α transcriptional activity in HRE luciferase reporter assay under hypoxia**

Investigators: Shuai Zhao and Wafik S. El-Deiry

Drug Development

Small molecule AMG-232 sensitizes high MDM2-expressing tumor cells to T-cell-mediated killing.

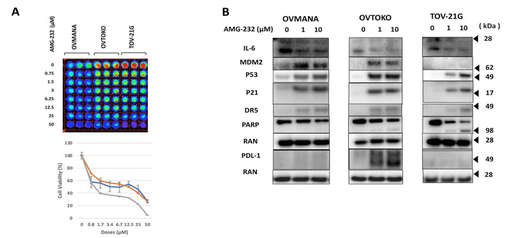


Figure 4. **Validation of AMG232 antitumor effect and the restoration of p53 signaling.**
Collaborators: Sahin L. Dizon D., Safran H., and El-Deiry W.S
Funding: the LCC Pilot fund award. (to S.L.)
Citations: 44 citations

Drug screening for the combination treatment in the tumor microenvironment

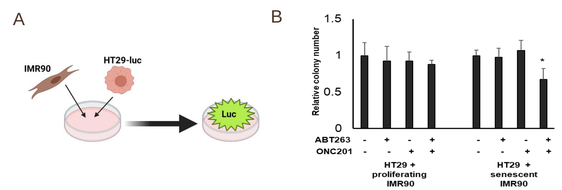


Figure 5. **The ongoing project for drug screening using a two-cell coculture system.**

Investigators and Collaborators: Shengliang Zhang, Kelsey E. Huntington, Lanlan Zhou, Bianca Kun, Jill Kreiling, John Sedivy, Wafik S. El-Deiry

Screening and prioritizing the FDA-approved drugs that synergize with the novel drug to kill brain tumor cells

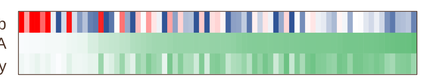


Figure 6. **Prioritization of the FDA approved drugs in the ongoing project for developing a novel strategy to increase the antitumor efficacy by the drug combinational treatment**

Collaborators: Sean Lawler and Jasmine Clark

Publications

Key Publications (2020-2023)

Impact on Users

Total Users: 11 laboratories

Cancer Center Members Users: 8 (72.72%)

Three members from the Cancer Biology program: Dr. Sedivy J. , Dr. Elias J.A. and Dr. Sobol R.W.

Five members from the Cancer therapeutics program: Dr. El-Deiry W.S., Dr. Safran H., Dr. Sahin L, Dr. Lawler S., Dr. Carneiro B.A.

Members with Peer-Reviewed Funding : 6 (54.5%)

Future Plans

- Assist Investigators with design of drug screens
- Provide technical support for high throughput screening
- Assist with grant submission
- Increase user base
- Interaction with other shared resources
- Become a self-sustainable service research facility